

infundibular passages, they are also present in the caseous areas, in the neighbourhood of the phthisical cavities, and some can be demonstrated in the fibrotic areas surrounded by definite fibroblasts. One in particular (see Fig. 12) measured about 75  $\mu$ . It is clear and segmented in its middle part, but the extremities are nodular and clubbed. It is difficult to imagine that a foreign body of such length could be transported by phagocytes, but they may represent larger bodies left in a bronchus which has become obliterated. The bodies have been examined with the micro-spectroscope, but so far no clue as to their nature has been obtained by this means. They are not refractile by polarized light.

#### *Nature of the Bodies.*

We have shown these preparations to several pathologists, but the appearances are new to them. To confirm our own opinion we have submitted them to experts in zoology, who are unanimous that they are not of animal nature. We have also submitted them to botanical and chemical authorities, and though there has been a considerable difference of opinion, some regarding them as hyphomycetes, the general opinion has been that they are not vegetable forms.

The fact that exactly similar bodies have been found in the lungs of another asbestos worker, and, so far as I can ascertain, have not been found elsewhere, would seem to indicate that they are essentially derived from or associated in some way with the asbestos itself. It is also certain that they do not in any way resemble concretions, largely composed of calcium and other salts, and also containing iron derived from blood, such as have been described as streptothrix forms in the spleen, and which may closely simulate mycelial filaments. The hypothesis advanced is that these bodies are portions of asbestos fibres in the process of alteration and absorption by hydrolysis, either by direct chemical action or by enzymes. The particular variety of asbestos with which this patient worked was a Canadian serpentine (chrysotile). It would probably contain silica and a magnesium salt in about equal proportions (40 per cent.) with up to 3 per cent. ferrous oxide, 1 per cent. of alumina, and water. From its high resistance to heat we are apt to regard asbestos as indestructible, but, given time, it is possible for hydrolysis of such silicates to occur, even in pure water. Such hydrolysis would be hastened and intensified by the presence of  $\text{CO}_2$  in the pulmonary alveoli, and the warm moist atmosphere there would, no doubt, accelerate the process. Even under these conditions the process would necessarily be a slow one. The magnesium could be separated out as relatively insoluble carbonate, or more soluble bicarbonate, which in turn would be converted into any other salt for which there happened to be the appropriate acid available.

The iron existing in a ferrous condition in the presence of an oxidizing agent might be converted into the ferric state, and subsequently precipitated as hydroxide. The silica might pass into a colloidal state, at first in sol form (orthosilicic acid), later passing into a gel (metasilicic acid). If this were so in sol form, it would tend to remain associated with the surface of the asbestos fibre by adsorption, and might be held there till it became a gel. In time the gel might adsorb the solution, and so gradual conversion of the fibre into a mass of gel would occur. There might be in the tissues sufficient albuminoid material to effect rapid gelatinization of the sol, particularly if, as would be the case here, the sol was being slowly produced. The fact that the gel is of high surface tension, and formed at an irregular rate, would give it a spheroidal structure and account for some of the appearances seen here. Whether this be the exact explanation or no, it is at least an hypothesis which should be capable of experimental verification. As has been held by Gye and others, in cases of silicosis there may be a direct chemical action of silica on the tissues apart from the merely mechanical irritation of the particles, with the production of fibrosis. Orthosilicic acid is, as has been shown, an active poison, but rapid conversion into metasilicic acid would minimize its action.

As to the relative part played by the asbestos and the

tuberculous infection in this case, in relation to the fibrotic change, it is difficult to say, but it is a reasonable assumption that the tuberculosis was a superadded infection, and in Dr. Grieve's case referred to above there was in the sections examined a considerable degree of fibrosis without apparent tuberculosis. The immediate cause of death in that case was a terminal broncho-pneumonia. Till some experimental work is completed the exact nature of these foreign bodies must remain in doubt, but their highly characteristic appearance may well prove to be an important diagnostic point in the recognition of the lung of a worker in asbestos.

I am much indebted to Dr. Cooke for material from his case, to Dr. Grieve for an opportunity of examining his microscopical sections, to P. L. Robinson, D.Sc., of the Chemical Department, Armstrong College, for his advice and suggestions on the chemistry of the silicates, and to Professor W. H. Lang, F.R.S., of Manchester, for a reasoned opinion as to the non-botanical nature of the foreign bodies.

## CLINICAL ASPECTS OF PULMONARY ASBESTOSIS.

BY

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DR. W. E. COOKE has given a short account of the history of asbestos, also of the processes of its manufacture into cloth-like structures much in the same manner as raw cotton fibre is woven. He has told us that in the carding department a considerable quantity of dust is evolved. The crushing of the rock is not carried on to any extent in this country; this is usually done in the countries where the mineral is quarried. Canadian rock is crushed in Canada so as to reduce the expense of transport to Great Britain. Our workers are therefore less exposed to the harmful influence of the dust—a fortunate circumstance, since the rock frequently contains as much as from 50 to 60 per cent. or more of silica.

With the exception of Dr. Cooke's paper on pulmonary asbestosis published in 1924, and the details of a fatal case published by Dr. Montague Murray in the *Charing Cross Hospital Gazette* in 1900, there has not been, to my knowledge, anything written in this country upon the subject. I have had, however, the opportunity of visiting asbestos factories in America, and of seeing cases of pulmonary asbestosis through the kindness of Drs. Haddow and Grieve of Armley, Leeds. It may, I think, be safely said that there must have been several deaths of workers in British factories from the malady, but as no autopsy and microscopical examinations of the lungs were made the deaths were probably certified as pulmonary tuberculosis.

Asbestos manufacture is largely a familial occupation. It has been carried on in this country only for a little over thirty years. Carding and spinning of the fibre are important processes in the manufacture of asbestos goods. In these departments many women are employed, mothers being succeeded by their daughters. Where ventilation of the carding and spinning rooms is properly attended to the atmosphere is fairly clear of dust and floating fibre, otherwise in these operations considerable quantities of dust become suspended in the atmosphere. In a British factory the dustiest process is "hand beating" of the finished mattresses used for covering and protecting the internal machinery of automobiles. This work should only be undertaken in a room separated from the main parts of the factory, with open windows at one end and strong down-draughts at the other, but even with this precaution men working therein should wear masks.

Recently, with Dr. Grieve of Armley, I examined two women who are the subjects of pulmonary asbestosis, one aged 48 and the other 39. The older patient was one of the first to commence work thirty years ago in the particular factory I visited. At that date no danger from dust was anticipated, so that no effective ventilation of the workrooms was attempted, such as prevails to-day. Although only 48 the first patient mentioned looks older by several years, and is extremely emaciated. She gave up work a year ago on account of increasing physical

debility, shortness of breath, and cough. At present she has no expectoration; her respiratory capacity is one inch. Although the apices of both lungs in front are resonant, there is distinct flattening of the percussion note at the bases. The respiratory murmur at the apices and mid-lung is coarser than usual, and the expiratory murmur is prolonged. At the right base the respiratory murmur is feeble, and small dry friction sound is heard. Towards the base of the left lung and extending into the axilla are heard small moist tinkling sounds, suggestive of cavitation having taken place; here also small friction sounds can be heard. Similar physical signs prevail posteriorly. The apex beat of the heart is displaced upwards and outwards; it is felt external to the nipple, a circumstance which, combined with marked accentuation of the second sound of the heart heard over the pulmonary artery, suggests that fibrotic changes have already occurred in this lung. Although the patient states that she has no expectoration, this was present six weeks ago, and when examined was found to be free of tubercle bacilli. There is no enlargement of the external glands.

The other patient, aged 39, has been an asbestos worker for eighteen years. She had no illness until four years ago, when she developed cough and attacks resembling bronchial asthma. After remaining away from the factory for three months she returned to her employment, and followed the occupation for three years, when she married, and as in the early months of her pregnancy she lost considerably in weight she retired from the factory. Although reduced considerably in weight, and the subject of cough all through her pregnancy, her infant daughter, who is 14 months old, is healthy and well developed.

The patient complains of a dragging in the chest without actual pain. There is noticeable shortness of breath on slight exertion, and she complains of morning cough with expectoration. The sputum has been examined and is negative as regards tubercle bacilli. Her appetite is poor. She weighs 8 st., a drop of 3 st. having occurred within the last two years. Her heart is healthy; the apex beat is not displaced, but the second sound over the pulmonary artery is distinctly accentuated. The apices of her lungs are resonant. Here the respiratory murmur is coarser than usual and the expiratory is prolonged, so that the inspiratory and expiratory murmurs approach each other in equality. Moist râles are heard in mid-axillae and small friction with crepitation is heard at the bases. This woman's mother, who is aged 60, is still working in the factory.

From what I have seen clinically of pulmonary asbestosis it resembles silicosis of the lungs in the marked shortness of breath on slight exertion, deficient respiratory capacity, physical debility, and, in examination of the sputa of not too far advanced cases, absence of tubercle bacilli, but since fibrotic changes are developing in both of the patients to whom I have alluded, there is almost sure to develop, if such has not already taken place, pulmonary tuberculosis.

The clinical picture of pulmonary asbestosis differs slightly from that presented by a patient the subject of ordinary tuberculosis of the lungs, in so far as there is a pronounced deadening of the skin varying from mild bronzing to slight blueness, a degree of shortness of breath in excess of the physical signs, a greater amount of general disability, little expectoration, and comparative absence of night sweats.

## AN ACTIVE CONSTITUENT OF THE PREPARATION CALLED "GLUKHORMENT."

BY

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AND

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IN May of this year Professor von Noorden published in the *Klinische Wochenschrift* an account of a new pancreatic preparation which had a controlling effect on carbohydrate metabolism, but, unlike insulin, was effective when administered by the mouth.<sup>1</sup> To this preparation the name "glukhorment" had been given, and the title of the paper made it clear that the substance was regarded by the author as containing a new anti-glycosuric principle, naturally preformed in the body. On information, evidently supplied to him by the chemist responsible for devising "glukhorment," Professor von Noorden stated explicitly that, in spite of indications in the patent specification, which might suggest some connexion of the active principle with a guanidine derivative, no such derivative, and in particular no synthalin,\* had been added; and, further, that the finished preparation contained no guanidine derivative of any kind in recognizable amount. Professor von Noorden drew the cautious conclusion that, if the activity were due to a guanidine derivative, it would have to be one of extremely high activity. In July of this year one of us (H. H. D.) received a communication from the Horment Company, who were manufacturing glukhorment, stating that they were sending material in the hope that clinical trials of it could be arranged. In due course this and several subsequent consignments of glukhorment were sent by the Horment Company, with a request for their trial.

A consideration of preliminary reports, on the mode of action of this preparation on the human being and on laboratory animals, suggested a strong similarity between its effects and those with which we had become familiar, through experiments then for some time in progress, on the action of synthalin. Some of the glukhorment

was immediately placed in the hands of one physician, who will presumably report his experience with it in due course. The physiological resemblance to synthalin was so pronounced, however, that, before the question of wider clinical trials was considered, it was thought desirable to make a simple chemical examination, in order to confirm the fact that the preparation was free from synthalin and similar guanidine derivatives, as stated in the paper by Professor von Noorden, of which copies had been submitted by the Horment Company in support of their request. The result of this first test showed clearly that a guanidine derivative strongly resembling synthalin was present in substantial amount in the glukhorment tablets as submitted for trial. The evidence thus early obtained was at once so clear and so surprising that it was considered desirable to use a further quantity of the material submitted, in order to obtain precise information as to the nature of the substance in question. The isolation of the substance was made easy by the fact that the nitrate of synthalin is a remarkably insoluble salt.

### *Chemical Isolation from Glukhorment of a Guanidine Derivative closely resembling Synthalin.*

Two hundred glukhorment tablets were powdered; the powder, weighing 60 grams, was thrown into 1 litre of boiling water and the mixture was kept gently boiling for fifteen minutes. The liquid was then filtered, while still hot, from a large mass of insoluble protein.

The filtrate was evaporated *in vacuo*, with the addition of octyl alcohol to prevent frothing, to a volume of 120 c.cm. On standing, it set to a jelly; this was warmed to 40°, when it became fluid, and concentrated nitric acid was added until the reaction of the liquid was strongly acid to Congo red. A white crystalline nitrate separated from the solution on standing, and the liquid no longer set to a jelly when cold. The crystalline material was collected by centrifuging, washed in the centrifuge with a small quantity of dilute nitric acid, and dissolved in about 25 c.cm. of hot water. This solution was boiled with charcoal and filtered. To the hot filtrate 0.5 c.cm. of 6 per cent. nitric acid was added, and the nitrate crystallized on cooling. This was filtered off and dried; it weighed 1.135 grams. It was then converted into the picrate by dissolving it in water and adding a saturated solution of sodium picrate until no further precipitate was produced. The picrate was filtered

\* "Synthalin" is the synthetic compound, decamethylenediguanidine, introduced by Frank, Nothmann, and Wagner, as an antidiabetic remedy for oral administration, and already the subject of numerous reports.